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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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EXAMINER

ART UNIT	PAPER NUMBER
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DATE MAILED:

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Advisory Action

Application No.

08:366,083

Applicant(s)

Pomerantz et al.

Examiner

Terry A. McKelvey

Group Art Unit

1636



THE PERIOD FOR RESPONSE: [check only a) or b)]

a) expires _____ months from the mailing date of the final rejection.

b) expires either three months from the mailing date of the final rejection, or on the mailing date of this Advisory Action, whichever is later. In no event, however, will the statutory period for the response expire later than six months from the date of the final rejection.

Any extension of time must be obtained by filing a petition under 37 CFR 1.136(a), the proposed response and the appropriate fee. The date on which the response, the petition, and the fee have been filed is the date of the response and also the date for the purposes of determining the period of extension and the corresponding amount of the fee. Any extension fee pursuant to 37 CFR 1.17 will be calculated from the date of the originally set shortened statutory period for response or as set forth in b) above.

X Appellant's Brief is due two months from the date of the Notice of Appeal filed on 2/7/00 (or within any period for response set forth above, whichever is later). See 37 CFR 1.191(d) and 37 CFR 1.192(a).

Applicant's response to the final rejection, filed on 2/7/00 has been considered with the following effect, but is NOT deemed to place the application in condition for allowance:

X The proposed amendment(s):

will be entered upon filing of a Notice of Appeal and an Appeal Brief.

X will not be entered because:

X they raise new issues that would require further consideration and/or search. (See note below).

they raise the issue of new matter. (See note below).

X they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal.

they present additional claims without cancelling a corresponding number of finally rejected claims.

NOTE: Entry of the amendments to the claims would necessitate new rejections under 35 USC 112, 2nd paragraph because of the addition of typographical errors in various claims such as 40 (several words are improperly and unclearly run together). Also, the amendment is in an improper format, newly added words are not underlined as required.

Applicant's response has overcome the following rejection(s):

Newly proposed or amended claims _____ would be allowable if submitted in a separate, timely filed amendment cancelling the non-allowable claims.

X The affidavit, exhibit or request for reconsideration has been considered but does NOT place the application in condition for allowance because:

the rejection is maintained for reasons of record because the applicants did not present new and convincing arguments. See the attachment.

The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

X For purposes of Appeal, the status of the claims is as follows (see attached written explanation, if any):

Claims allowed: _____

Claims objected to: _____

Claims rejected: 40-70 and 72-98

The proposed drawing correction filed on _____ has _____ has not been approved by the Examiner.

Note the attached Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

X Other: also note, the response to the final rejection improperly failed to include cancellation of the non-elected claims

TERRY A. MCKELVEY
PRIMARY EXAMINER
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ATTACHMENT TO THE ADVISORY ACTION

The new arguments not previously presented are addressed below. The other arguments as they apply to arguments previously discussed, are addressed in the previous office actions.

The applicant argues that Park et al did not intend the general statements made in the cited reference to be given the broader interpretation reflected in the office action, citing several lines of evidence:

1. A later reference referring to the cited reference, defining the concept of "protein stitchery" (more narrowly).
2. Park et al limited themselves to proteins which bind along the minor groove, when clearly there are DNA binding proteins which bind along the minor groove and indeed, homeodomains and zinc finger domains do make minor groove contacts.

These arguments are not persuasive for the following reasons. First, the later reference referring to a more narrow definition of protein stitchery is not persuasive that the Park et al general teachings are not meant to be interpreted broadly by one of ordinary skill in the art because most of the Park et al reference cited in the rejection is drawn to teaching one particular embodiment, which is making the chimeric protein from

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the arms of a dimer. That is what is being referred to in the second Park et al reference, because that specific embodiment is further explored in that reference. Thus, naturally the same particular embodiment would be referenced in the second publication in that fashion. This does not mean that the other broad teachings of the cited Park et al reference are to be ignored or interpreted in a way much narrower than the actual statements because it is well established that references must be considered for all of what they teach, which means that in the instant case, even though most of the reference applies to the more narrow embodiment, the teachings elsewhere in the reference that are clearly much more broadly applicable must also be considered. It is these broader teachings, in combination with the other cited teachings that would suggest to one of ordinary skill in the art the claimed invention. The fact is that the cited teachings are specifically generic: "We propose a general strategy for designing proteins ... select segments of proteins, each of which recognizes particular DNA segments and to stitch these segments together ...". [Instant underlining added for emphasis.] If the reference had intended a more narrow interpretation to the specific embodiment described, then the much broader terms would not have been used, instead the description of stitching together dimer arms would have been used. But, that wasn't done. It is the examiner's contention

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that the broader language was specifically used and meant to be interpreted accordingly. In fact, in further support of the broader interpretation, the first sentence of the paragraph immediately after the cited section states: "As a starting point, we consider the gene-regulatory leucine-zipper proteins." This shows that the more narrow embodiment that is taught is the starting point for the general strategy, i.e., an example of the general principle broadly set forth in the reference. It is clearly not intended to be a teaching of the only embodiment possible for the general strategy that is taught.

With regard to the second line of evidence, this argument is not persuasive because it is and was well known in the art that the vast majority of sequence-specific DNA-binding domains make their most important, sequence-specific contacts to the DNA in the major groove, not the minor groove. It is the first and last part of the cited sentence that is most important: "Any protein or other molecule that recognizes a specific DNA sequence ... could be a candidate". The rest of the sentence, "by binding along the major groove" merely recites what is and was well known in the art, that recognition of a specific DNA sequence occurs by binding along the major groove. It is and was well known in the art that although some DNA binding domains make some contact with the minor groove, the predominant, sequence-specific contacts are made in the major groove. It is the non-sequence specific DNA

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binding domains which are known in the art to bind in some cases predominately to the minor groove which are clearly excluded from the teachings of the reference because of the lack of sequence-specific binding. Such non-sequence-specific binding goes against the purpose of the reference, to design a protein for selective binding to a specific DNA sequence.

The applicant also argues that the following belies acceptance in the art of the broader conclusions from the Park et al reference: the publication of the applicant's work in Science. The response to this argument is discussed below.

The applicant also argues that the nether of the Harrison and Mitchell et al references refer to portions of DNA binding domains, e.g. individual zinc finger domains, which can also constitute part of the applicant's claimed invention. This argument is not persuasive because the applicant is arguing a limitation that is not present in the claims, that the two parts of the chimeric protein that are responsible for binding to the final composite binding site can be "portions" of DNA binding domains. The actual limitations which the applicant appears to be referring to merely indicates that the nucleic acid binding domains (which is only properly read as whole nucleic acid binding domains) include a particular motif (open language), not that they consist of a particular motif (closed language) which when closed only reads on a portion of a nucleic acid binding

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domain. The art rejections of record are not based upon the obviousness of combining portions of nucleic acid binding domains together, and in fact, such a limitation probably would overcome the art rejections, necessitating further consideration and search (and thus, because of the need for further consideration and search and due to the After-Final status of the instant case, such an amendment would not be entered, except when filed with a continuation case or a CPA request).

With regard to the applicant's discussion of the basis of the reasonable expectation of success, it was previously discussed in detail. The combined teachings of the cited references provides the reasonable expectation of success, not the Harrison or Mitchell references by themselves. The main source is the Park et al reference which shows that a chimeric protein can be made by fusing together two nucleic acid binding domains that separately binds to half of the composite site recognized by the fusion, resulting in a protein that binds to the composite site (which of course, by preferentially binding to the composite site, does so at a higher affinity than binding to either of the original individual sites). The Harrison and Mitchell references show that there would be a reasonable expectation of success of obtaining the nucleic acid binding domains as discrete domains for use in the general strategy taught by Park et al. The applicant also questions the

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reasonable expectation of success that binding of the chimeric protein containing a transcriptional activation domain to a DNA binding site would be able to stimulate transcription of a target gene. This argument is not persuasive because it is and was well known in the art that transcriptional activation could be achieved by linking the transcriptional activation domain to a heterologous DNA binding domain in order to achieve DNA binding site dependent transactivation; this was taught by Gossen et al, which reference provides reasonable expectation of success for achieving such activation in an analogous chimeric protein made from the combined teachings of the cited references.

The applicant also argues that the statement by the inventor of the instant application after publication in Science, "laboratory tests have proved the artificial switch can find, and control, a single gene among the 80,000 that exists in humans.", and another author's quote "the critical thing was showing it can find the proper site.", and that if there had been a reasonable expectation of success, the paper couldn't have been published. These arguments are not persuasive because "reasonable expectation of success" is a legal standard which is not the same as the standard applied to determination of whether something is or is not to be published. Publication is based upon other factors and novelty in the art, which is not argued as shown by the lack of a rejection under 35 USC 102, not whether or not

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other references in the art in combination suggest the claimed invention, as per the Graham v. Deere analysis of obviousness. This also applies to the cited comments which essentially discuss whether the novel findings that were published actually operate. These comments have no bearing on whether the particular combination of teachings of the cited reference legally make obvious the claimed invention and provide a reasonable expectation of success.

The applicant also argues that although Park et al teach that a peptide bond can link the two DNA binding domains, a person of skill in the art would have known that a peptidic bond may give rise to a protein structure that is different from that resulting from disulfide cross-linking and thus there is no reasonable expectation of success. This argument is not persuasive because the Park et al reference specifically states that the linker is not essential in the design, and that they could just as well replace the cysteine and make a continuous protein that should recognize a predictable site. This teaching and the rest of the references provides the reasonable expectation of success. One of ordinary skill in the art would apply the relevant teachings of the cited art to make a single protein that had the specific peptide bonds which result in the functional chimeric protein.

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With regard to the rejection of the claims dependent on the additional Gossen reference, the applicant merely refers to the arguments set forth above with regard to the rejection lacking the Gossen et al reference. The arguments in response set forth above are equally applicable.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 23, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone numbers for the Group are (703) 308-4242 and (703) 305-3014.

NOTE: If Applicant does submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

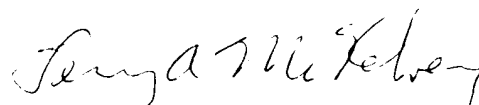
Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terry A. McKelvey whose telephone number is (703) 305-7213. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 6:30 AM to about 5:00 PM. A phone message

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left at this number will be responded to as soon as possible (usually no later than 24 hours after receipt by the examiner).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. George Elliott, can be reached on (703) 308-4003.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

February 14, 2000